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How to... Diagnose and Manage Proteinuria in Chronic Kidney Disease in Practice

Introduction

Chronic kidney disease (CKD) is one of the most commonly diagnosed diseases in cats and prevalence increases with advancing age, ranging from 31% to 81% in geriatric populations. Diagnostic work-up generally includes blood and urine testing, blood pressure measurement as well as imaging and should be performed in the presence of historical and clinical findings suggestive of CKD, such as lethargy, inappetence, weight loss, dehydration, polyuria/polydipsia, altered kidney size, systemic hypertension and urine specific gravity (USG) < 1.035. CKD management consists of diet modification, treatment of systemic hypertension and treatment of proteinuria as well as supportive and symptomatic treatments on a case by case basis. Although there is no treatment for CKD, early diagnosis and disease management in conjunction with home monitoring result in delay of disease progression and, ultimately, improved prognosis and quality of life.

Diagnosis and Staging of CKD

Following diagnosis, staging is performed according to the International Renal Interest Society (IRIS) guidelines. It is important to note that staging can only be undertaken in patients with normal hydration status and stable renal function by measuring fasting serum/plasma creatinine concentration (Table 1). Substaging is performed for urine protein creatinine ratio (UPC; Table 2) and systolic blood pressure (SBP; Table 3).

Table 1: IRIS Staging based on fasting blood creatinine concentration (µmol/l)

Stage	Creatinine	Clinical Comments
At risk	< 140	At risk of developing CKD based on history (age, breed, drugs)
Stage 1	< 140	Nonazotaemic. Other renal abnormalities, such as low USG, renal proteinuria etc present.
Stage 2	140 – 250	Mild renal azotaemia. Mild clinical signs (PU/PD) or absent.
Stage 3	251 – 440	Moderate renal azotaemia. Many renal and extra-renal signs.
Stage 4	> 440	Severe renal azotaemia. ↑risk of systemic signs and uraemic crisis.

Table 2: IRIS Substaging by Proteinuria (UPC)

Substage	Cats ^a
Non proteinuric	<0.2
Borderline proteinuric	0.2-0.4
Proteinuric	>0.4

^aNormal intact male cats can have a UPC ≤ 0.6.

Table 3: IRIS Substaging by Systolic Blood Pressure (mmHg)

Substage	Systolic Blood Pressure	Risk of Future Target Organ Damage
Normotensive	< 150	Minimal
Borderline Hypertensive	150 – 159	Low
Hypertensive	160 – 179	Moderate
Severely Hypertensive	≥ 180	High

Assessment of Proteinuria

It is estimated that 50-60% of cats with CKD are non-proteinuric, whilst overt proteinuria (UPC >0.4) is seen in approximately 20% of cats with CKD. Recognition and management of proteinuria is of paramount importance, as proteinuria has been strongly associated with CKD progression and survival. Assessment of proteinuria includes identification of its localisation, persistence and magnitude.

Localisation

The origin of proteinuria can be pre-renal, renal or post-renal.

- Pre-renal proteinuria results from the inability of the glomerulus, the filtration unit of the kidney, to absorb high quantities of specific proteins in disease processes such as multiple myeloma or intravascular haemolysis. Specific diagnostics such as serum protein electrophoresis need to be undertaken in addition to routine blood work to diagnose pre-renal proteinuria.
- Renal proteinuria can be functional or pathological. Functional renal proteinuria can be seen as a result of fever, seizures or strenuous exercise, although this is rarely recognised

in cats. Pathological renal proteinuria can be the result of damage in the glomerulus (glomerular proteinuria) or in the renal tubules and interstitium (tubulointerstitial proteinuria). Primary glomerular proteinuria is rarely seen in cats with CKD as they mostly exhibit tubulointerstitial proteinuria. Secondary glomerular proteinuria, on the other hand, is more common and occurs due to systemic hypertension. In these cases, management of hypertension will usually resolve the proteinuria.

- Post-renal proteinuria occurs as a result of exudative or haemorrhagic processes affecting the lower urinary or genital tract e.g. urinary tract infection. This can be excluded by performing urine sediment examination.

Persistence

Proteinuria is considered persistent if confirmed at least three times, two or more weeks apart.

Magnitude

Different methods can be used to assess the magnitude of proteinuria. These are either semi-quantitative, such as the “dipstick” or the Sulfosalicylic acid turbidimetric method (SSA) or quantitative, such as UPC and urine albumin.

The reagent pad colorimetric method, also known as “dipstick”, primarily detects albumin in the urine. Although it is widely available and easy to use, false positive and false negative readings can occur with highly concentrated urine, very acidic or alkaline urine or pigmented urine. Particularly in the cat, sensitivity is 90% and specificity is only 11% (Lyon et al., 2010).

The Sulfosalicylic acid turbidimetric method (SSA) performs better than the dipstick; however it cannot be run in-house and false positives or negatives can still occur.

Moreover, both dipstick and SSA results need to be interpreted in conjunction with the USG and sediment examination.

UPC should be performed in any cat with a positive dipstick reading either in-house or at a reference laboratory as it is considered the gold standard method of confirming and quantifying proteinuria. More specifically in cats, a single measurement in a free catch or cystocentesis sample correlates with 24-hour quantification (Adams et al., 1992), whilst there is excellent correlation between free catch and samples obtained via cystocentesis (Vilhena et al, 2015). As shown on Table 2, neutered cats are expected to have a UPC <0.2, however normal intact male cats can have <0.6, most likely due to the presence of urinary cauxin.

Urine albumin can be measured in a reference laboratory only, however the clinical benefit of measuring urine albumin: creatinine ratio (UAC) over UPC hasn't been demonstrated in cats (Jepson et al, 2009).

Management of Proteinuria

Based on current IRIS guidelines (Table 2), medical intervention for the management of proteinuria is needed in cats with a UPC >0.4. Nevertheless, some clinicians will advocate treatment of cats with borderline proteinuria, as non-proteinuric cats have been shown to have a better prognosis compared to cats with even borderline proteinuria.

Inhibition of the renin-angiotensin-aldosterone-system (RAAS) which is activated in CKD has been the main therapeutic target in the approach to reduce proteinuria. RAAS activation (Figure 1) promotes proteinuria and, in the long term, results in progressive renal injury. Agents targeting RAAS (Table 4) licensed for the management of proteinuria in cats with CKD are the angiotensin-converting enzyme inhibitor (ACEi) benazepril and angiotensin-receptor blocker (ARB) telmisartan. The aldosterone-receptor antagonist spironolactone can be used in dogs, whilst renin inhibitors are used in humans, but not dogs or cats.

Table 4: RAAS inhibitors licensed for the management of proteinuria in cats with CKD in UK

Class	Drug	Formulation	Initial dose
Angiotensin-converting enzyme inhibitors	Benazepril	Tablet	0.5-1.0 mg/kg PO q24hrs
Angiotensin receptor blockers	Telmisartan	Oral solution	1 mg/kg PO q24hrs

ACEi

The use of ACEi has been shown to significantly reduce proteinuria in cats. However, no survival benefit has yet been shown, although studies to date have had a small sample size.

Benazepril undergoes both renal and hepatic elimination which would be beneficial compared to enalapril with regards to safety when administered in cats with IRIS CKD Stage 3 or 4. However, there is no current evidence to suggest that one ACEi is superior to another and benazepril is the only ACEi licensed in the UK for the management of proteinuria in cats with CKD.

ACEi should only be administered in stable, euhydrated and normotensive cats and greater care should be taken in cats with IRIS stage IV CKD since their administration can result in hypotension, worsening of pre-existing azotaemia and, rarely, hyperkalaemia.

ARB

The AT-II type-2 receptor (AT₂) is considered to have renoprotective actions and angiotensin receptor blockers selectively inhibit AT₁, preventing

Losartan wasn't shown to be effective in reducing proteinuria in cats, however the study wasn't performed in patients with naturally occurring disease (Jenkins et al, 2015). Telmisartan is the only ARB licensed in the UK for the management of proteinuria in cats with CKD. In a study comparing benazepril and telmisartan, a greater decrease in UPC was observed over time in cats receiving telmisartan (Sent et al, 2015).

Combination Therapy

Combination therapy with an ACEi and an ARB may be indicated if either is not effective in reducing proteinuria. As there are no studies evaluating the safety of combination therapy in cats and care should be exercised as combination therapy increased risk of kidney failure and mortality in a subset of human patients.

Aldosterone Breakthrough

Aldosterone breakthrough refers to a phenomenon where serum aldosterone concentration increases over time even if maximal doses of RAAS inhibitors are received. In ACE-escape, on the other hand, there is ongoing AT-II production due to incomplete inhibition of conversion of AT-I to AT-II in patients administered ACEi. Both phenomena occur over time in a subset of human patients, but the mechanisms and incidence are unclear in cats. Consequently, as there are no published studies exploring the use of aldosterone receptor antagonists such as spironolactone in cats with proteinuric CKD, its use would be off licence and may be considered in a cat with high serum aldosterone concentration and persistent proteinuria despite treatment with ACEi and/or ARB.

Renal Biopsy & Immunosuppressive Therapy

Renal biopsy can provide information about the severity of underlying renal injury, but also potentially offer a definitive diagnosis. Contraindications to performing a renal biopsy include moderate or marked azotaemia, renal cystic disease, hydronephrosis, pyelonephritis, uncontrolled hypertension, severe anaemia or coagulopathy.

Renal biopsy is indicated in cats with proteinuria of high, glomerular-level magnitude that haven't responded to RAAS inhibition, however results of a renal biopsy are unlikely to alter long-term management in cats with CKD as it has been shown that over 50% have tubulointerstitial nephritis (Chakrabarti et al, 2012; DiBartola et al, 1987). Consequently, immune-mediated glomerulonephritis is considered rare in cats and immunosuppressive treatment should be considered only if this has been confirmed by performing a renal biopsy. It should be noted that no Renal Standardization Projects have been undertaken in cats to date and no consensus guidelines have been produced.

Adjunctive therapies

Dietary therapy: Feeding of renal diets is considered to decrease proteinuria, however they are rarely useful as a monotherapy.

Omega 3 (n3) and Omega 6 (n6) Polyunsaturated fatty acids (PUFA): In study evaluating the feeding of various renal diets to cats with CKD, all studied diets improved survival. Although the diet with the highest eicosapentaenoic acid (n3) content was associated with the longest survival, a causal relationship wasn't proven and therefore there are no specific dietary supplementations recommended like in dogs.

Antithrombotic therapy: Thromboembolism is often recognised in dogs but rarely in cats and, to the author's knowledge, there are no published studies in this species.

Treatment monitoring

A decreased UPC <0.4 is the optimal therapeutic target for proteinuric CKD in cats, although this is not achieved in many patients. Following initiation or a change in dose of RAAS blockade therapy, clinical signs, creatinine, urea and SBP should be measured after 5-7 days. Treatment modification consisting of ACEi or ARB dose reduction or cessation is indicated if there is an increase in serum creatinine of $>15\text{-}20\%$ suggesting worsening renal function.

Prognosis of Cats with Proteinuric CKD

Proteinuria is a negative prognostic indicator in cats with CKD and multiple studies have demonstrated that the magnitude of proteinuria is inversely proportional to survival. Although in humans and dogs the reduction of proteinuria has been shown to improve survival and delay disease progression, the same has yet to be demonstrated in cats receiving anti-proteinuric treatment.

Conclusion

Management of proteinuria in cats with CKD is achieved by administering drugs that inhibit the RAAS system. Regular assessment of clinical and laboratory parameters is indicated and treatment tailored accordingly and to the individual cat. Adjunctive treatments might also be helpful in the management of proteinuria, however more studies are needed to prove their benefit. Most cats with CKD have tubulointerstitial nephritis rather than glomerular disease and, therefore, a renal biopsy is rarely indicated. Although a survival benefit has not yet been demonstrated, RAAS inhibition is recommended in cats with overt proteinuria.

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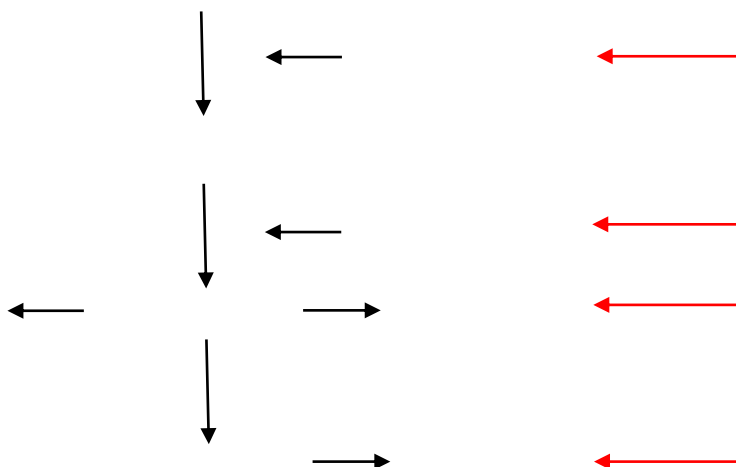


Figure 1. The renin-angiotensin-aldosterone-system and its inhibitors. ACE, angiotensin-converting enzyme, AT₁; angiotensin II type-1 receptor, AT₂, angiotensin II type-2 receptor.
*Aldosterone receptor antagonists and renin inhibitors are not currently used in cats.